REMARKS

Claim 7, 10, and 15-20 are currently under consideration in the above-referenced application. Although claims 8, 12, 14 and 22 have been withdrawn in view of the Restriction Requirement, Applicant asserts that these claims are subject to rejoinder upon indication of allowable subject matter under MPEP §821.04. Thus, these claims are still pending. It is still Applicant's position that claims 8, 12 and 22 constitute linking claims (linked to claim 7).

Claims 7, 12, 20 and 22 have been amended to more distinctly claim that which Applicant regards as the invention. The amendment of claim 7 is addressed below. Claims 20 and 22 have been amended to remove reference to Carboxypeptidase M (claim 20) and SEQ ID NO:3 (claim 22).

New claims 23-31 have been added to recite specific embodiments. These new claims are supported by the specification. No new matter has been added.

Claims 1-6, 9, 11 and 13 have been canceled in view of the Restriction Requirement. Applicant reserves the right to file subsequent continuation and/or divisional applications on the subject matter contained in the canceled claims.

1. Claim Objections

The following objections were made:

> Claim 7, with dependent claims 10 and 15-20, is objected to as dependent from non-elected claim 1.
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> Claim 7 is further objected to as reciting non-elected species.
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> Claim 19 is objected to as reciting 'SEQ ID NO3" instead of 'SED ID NO: 3".

In response, claim 7 is now an independent claim. Applicant notes that claim 7 recites the elected species. As will be discussed in further detail below, the term "splice junction" has been deleted and has been replaced with "contiguous exon-intron region" and "contiguous intron-exon region". As stated in the Office Action dated May 6, 2004, the Examiner indicated that claim 7 was a generic claim so the recitation of other species is allowable. Applicant does note that claims 24 and 25 have been added and read on the elected species.

Applicant further notes that claim 19 has been canceled.

In view of the above amendments and remarks, Applicant asserts that the claim objections have been overcome, Therefore, Applicant respectfully requests that the objection be withdrawn.

2. The Rejections Under 35 U.S.C. §112, First Paragraph-Written Description

Claims 7, 10 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action specifically states:

> Claim 7, with dependent claims 10 and 15-20, is drawn to a "nucleic acid molecule of at least 20 nucleotides that specifically hybridizes to a non-coding region of SEQ ID NO: 4. Claim 7 encompasses structurally diverse nucleotides because a non-coding region of claim 7 encompasses an intron, a splice junction, a 5'-non-coding region, an expression control element, a transcription factor binding region and a 3'-non-coding region. The claimed molecules are structurally diverse because they encompass molecules that hybridize to any splice junction of SEQ ID NO: 4. Furthermore, the function of the claimed at least 20 nucleotides is not defined (see the 112, 2nd paragraph rejection below).
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> Therefore, the genus of nucleic acid molecules that comprise these above nucleic acid molecules is a large variable genus with the potentiality of encoding many different proteins and encoding no proteins but having other functions. Therefore, many functionally unrelated nucleic acid molecules are encompassed within the scope of the claim, including partial nucleic acid sequences. The specification does not contain any disclosure of the function of all nucleic acid sequences that hybridize under high stringency to a non-coding region, including a splice junction of SEQ ID NO: 4. There are several known splice variants of SEQ ID NO: 4 (Sigalas et al. (1996) Nature Medicine, 2, 912-917, especially page 913). The specification discloses only splice sites for a single splice variant of SEQ ID NO: 4 from which splice junctions of this variant can be gleaned (page 10, Table 2). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties and fails to disclose the correlation between function and structure common to all members of the genus of splice junctions. Thus, one

skilled in the art cannot visualize or recognize the identity of the members of the genus.

One skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant respectfully traverses the rejection. As stated in the previous response, a representative number of species were disclosed in the specification. However, in order to advance prosecution, claim 7 has been amended to recite that the claimed nucleic acid molecule **consists of at least 20 nucleotides unique** to a reverse or forward strand of a non-coding region of SEQ ID NO:4, which non-coding region is selected from the group consisting of an intron, a 5'- non-coding region depicted in nucleotides 51039-41739 of SEQ ID NO:4, a 3'-non-coding region depicted in nucleotides 9503-1 of SEQ ID NO:4, a contiguous intron-exon region and a contiguous exon-intron region. The amendment of claim 7 is not acquiescence to the Examiner's position. Applicant reserves the right to file subsequent continuation and/or divisional applications directed to subject matter canceled in claim 7. Applicant notes that amended claim 7 is supported by the specification, e.g., on page 3, lines 10-28 and the paragraph bridging pages 9 and 10 and encompassing Table 2. Additionally, claims 10-15 and new claims 23, 26-28 and 30-31 which depend from claim 7 are supported by the specification as well.

As noted previously, new independent claim 24, directed to an isolated nucleic acid molecule consisting of at least 20 nucleotides unique to a reverse or forward strand of a contiguous exon-intron region or a contiguous intron-exon region has been added. New claim 24 like claim 7 is supported by the specification. Claim 25 depends from claim 24. It is Applicant's assertion that claims 24 and 25 fulfill the written description requirement.

Furthermore, Applicant has added new claim 29 which is directed to a nucleic acid molecule consisting of between 20 and 5000 nucleotides or its reverse strand that hybridizes at 55°C, 5X SCC to a non-coding region unique to SEQ ID NO:4 or its reverse strand, which non-coding region is selected from the group consisting of an intron, a 5'- non-coding region depicted in nucleotides 51039-41739 of SEQ ID NO:4, a 3'-non-coding region depicted in nucleotides 9503-1 of SEQ ID NO:4, a contiguous intron-exon region and a contiguous exon-intron region. New claim 29 is supported by the specification as well, e.g., page 3, lines 10-

28, the paragraph bridging pages 7 and 8, and the paragraph bridging pages 9 and 10 and encompassing Table 2.

It is Applicant's position that the subject matter recited in amended claim 7, pending claims 10, 15-20 and new claims 23-31 are adequately described in the specification. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. §112, first paragraph (written description) be withdrawn.

3. The Rejections Under 35 U.S.C. §112, First Paragraph-Enablement

Claims 7, 10 and 15-20 have been rejected under 35 U.S.C. 112, first paragraph. In the Examiner's view, the specification, while being enabling for a non-coding region of at least 20 nucleotides of SEQ ID NO:4, does not reasonably provide enablement for at least 20 nucleotides that specifically hybridize to a non-coding region, including splice junction, of SEQ ID NO: 4 and have no known function. It is concluded that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Applicant respectfully traverses the rejection for reasons noted in the response to the previous Office Action. However, as stated above, claim 7 has been amended to more distinctly claim that which Applicant regards as his invention and in particular to advance prosecution. Claims 10 and 15-20 depend from claim 7. Furthermore, it is Applicant's position that new claims 23-31 are enabled by the specification as well. In particular, Applicant notes that claim 24, directed to an isolated nucleic acid molecule consisting of at least 20 nucleotides unique to a reverse or forward strand of a contiguous exon-intron region or a contiguous intron-exon region has been added.

In view of the above arguments and amendment to claim 7, Applicant asserts that the rejections under 35 U.S.C. §112, first paragraph (enablement) has been overcome. Therefore, Applicant respectfully requests that the rejection be withdrawn.

4. The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 7, 10 and 15-20 have been rejected under U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Office Action specifically states:

Claim 7 is drawn to "an isolated nucleic acid molecule of at least 20 nucleotides that specifically hybridizes to a non-coding region of the nucleic acid molecule of claim 1. The terms 'specifically hybridizes" is not defined in the specification where hybridization are given by non-limiting examples (page 8). Furthermore the term "splice junction" is not defined in the specification (page 9, line 32). It can be gleaned that splice junction should comprises junction between intron and exon. As mentioned above the specification teaches 5' and 3' splice sites (Table 2). However, it is not defined how many nucleotides on each side of exon-intron junction it comprises. Furthermore, claim 7 recites a non-coding region that is a splice junction. It is confusing because it can be construed as directed to only a non-coding, i.e. intron part of a splice junction. Further, claim 7 depends from claim 1, which in its turn is unclear. For example, the metes and bounds of the term "variant" are unclear. It is unclear the difference between a nucleic acid and its "reverse complement". The metes and bounds of the term 'complement: are not clearly defined and include fully and partially complementary sequences (page 8, lines 10-17).

Claim 19 depends from claim 18. Claim 18 is drawn to "The solid support of claim 17 wherein said support is a microarray". Claim 19 is drawn to "The solid support of claim 18, wherein said microarray further comprises a plurality of nucleic acid molecules hybridizing to a non-coding region of SEQ ID NO 3 or 4". The limitation in claim 19 appears to be redundant because the microarray comprises a plurality of nucleic acid molecules hybridizing to a non-coding region of SEQ ID NO: 4.

In response, Applicant notes that claim 7 has been amended to advance prosecution. Specifically, the phrases "specifically hybridizes". "splice junction", "variant" and "reverse complement" are no longer present. Applicant notes that amended claim 7 and new claims 24, 26, 27 and 29 recite "contiguous exon-intron region" and "contiguous intron-exon region". Claims 10, 15-20, 23, 26-28 and 30-31 depend from claim 7.

Applicant notes that claim 19 has been canceled. New claims 30 and 31 are directed to a microarray. In particular, claim 30 is directed to a microarray comprising a plurality of the nucleic acid molecules of claim 7. New claim 31, which depends from claim 30 recites that the microarray further comprises a nucleic acid molecule encoding human mouse double minute 2 homolog, complementary sequence thereof or a portion of said nucleic acid

molecule containing at least 20 nucleotides.

Therefore, in view of the amendment to claim 7 and the above arguments, Applicant asserts that the rejection under 35 U.S.C. §112, second paragraph has been overcome. Therefore, Applicant respectfully requests that the rejection be withdrawn.

5. The Rejections Under 35 U.S.C. §102(b)

Claims 7, 10 and 15 are rejected under 35 U.S.C. 102 (b) as being anticipated by Muzny et al. The Office Action states:

> Muzny et al. (GenBank accession AC025423, March 9, 2000) teach the sequence of human chromosome 12 comprising the sequence of SEQ ID NO: 4. Said sequence would hybridize to a fragment thereof that is a non-coding region, including splice junction. To be sequences and submitted to GenBank database, the DNA should be inserted in a vector that can be considered as a composition comprising said DNA and a carrier.
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> Claim 15 is included herein because "A kit" con be construed as a preamble that does not limit the scope and has no patentable weight.

Applicant respectfully traverses the rejection. Claim 7 would not be anticipated by Muzny et al. since Muzny et al. discloses the sequence of the genomic clone AC025423 in its entirety, which certainly contains more than sequences unique to a non-coding region of SEQ ID NO:4. Nevertheless, claim 7 has been amended in order to advance prosecution. As amended, claim 7 is now directed to a nucleic acid molecule consisting of at least 20 nucleotides unique to a non-coding region of SEQ ID NO:4. Applicant notes that claims 10, 15-20 and new claims 23, 26-28 and 30-31 depend from claim 7 and would also not be anticipated by Muzny et al.

Applicant further notes that in particular, new claim 24 is directed to an isolated nucleic acid molecule consisting of at least 20 nucleotides unique to a reverse or forward strand of a contiguous exon-intron region or a contiguous intron-exon region. There is no disclosure in Muzny of a nucleic acid molecule unique to a non-coding region of SEQ ID NO:4 or particularly an isolated nucleic acid molecule consisting of at least 20 nucleotides unique to a reverse or forward strand of a contiguous exon-intron region or a contiguous intron-exon region. Claim 25 depends from claim 24 and would not be anticipated by Muzny et al.

It is Applicant's position that claim 29 would also not be anticipated by Muzny et al. since these claims are directed to a 20-5000 nucleotide nucleic acid molecule.

In view of the above arguments, the amendment of claim 7 and new claim 24, Applicant asserts that the rejection under 35 U.S.C. §102(b) has been overcome. Therefore, Applicant respectfully requests that the rejection be withdrawn.

6. The Rejections Under 35 U.S.C. §103(a)

> Claims 7, 10, and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al, in view of Vogelstein et al.
>
> The teachings of Muzny et al are outlined above.
>
> Vogelstein et al (US Patent 5,411,860 GenBank accession NM_002392) teach cloning functional expression and chromosomal localization of human mouse double minute (MDM2) homolog. They teach cDNA (SEQ ID NO: 1) encoding human MDM2 homolog (SEQ ID NO: 2) that is 100% identical to the human MDM2 homolog of the instant invention (SEQ ID NO: 2). They a labeled probe, they localized the gene encoding said human MDM2 homolog to chromosome 12q12-14 (citations omitted).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use said cDNA to identify the genomic DNA that encodes the human MDM2 homolog of SEQ ID NO: 2 on chromosome 12q12-14. The state of the art provides various techniques for obtaining genomic DNA using cDNA probes that are usually labeled. The comparison of genomic and cDNA would result in the identification of non-coding regions. One of ordinary skill in the art would have been motivated to use said non-coding regions or fragments thereof of at least 20 nucleotides for detecting variants of chromosome 12q12-14 from genomic nucleotide samples from an individual, for example. As a matter of convenience a non-coding region such as a splice junction or fragments thereof can be present in a kit or on a solid support. Further, said support can be a microarray to a customary use of nucleic acid molecules in the art.

Applicant respectfully traverses the rejection. A finding of obviousness under 35 U.S.C. §103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and prior art, the level of ordinary skill in the art, and whether

the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere,* 383 U.S. 1 (1966). Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires analysis of the prior art as to whether there is a teaching, motivation or suggestion to select and combine the references relied on as evidence of obviousness. *McGinley v. Franklin Sports, Inc.,* 262 F.3d 1339, 60 U.S.P.Q.2d 1001 (Fed. Cir. 2001) and *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

It is applicant's position that one of ordinary skill in the art would not be motivated to combine the disclosures of Muzny et al. and Vogelstein et al. to obtain the claimed nucleic acid molecules of the present invention, a nucleic acid molecule consisting of at least 20 nucleotides unique to a noncoding region of SEQ ID NO:4, human mouse double minute 2 (MDM2) genomic DNA and in particular, an isolated nucleic acid molecule consisting of at least 20 nucleotides unique to a reverse or forward strand of a contiguous exon-intron region or a contiguous intron-exon region of SEQ ID NO:4.

Vogelstein et al. merely discloses the cDNA sequence of MDM2; it contains 2372 nucleotides. Muzny et al. discloses the sequences of AC025423 (150,579 nucleotides). Therefore, the cDNA constitutes only 1.6% of the sequence present on AC025423. No direction is provided in these references regarding the genomic organization of the MDM2 gene and particularly, the number and size of exon and intron sequences, location of exon-intron and inton-exon regions and the size of the 5' and 3' noncoding regions.

There was also no indication provided in the cited references regarding the position of the noncoding sequences and particularly, contiguous exon-intron or intron-exon regions within AC025423 with respect to the MDM2 gene. Muzny et al. did not recognize that the gene was present in this clone. The human MDM2 genomic sequence was unexpectedly found to contain at least 10 exons. There is a vast range in the size of the introns ranging from 126 bases to about 7 kB. There is also a significant range in the size of the exons, ranging from 51 bases to 573 bases. Again as noted above, no teaching was provided with respect to the size or location of the noncoding or coding sequences of MDM2 within AC025423.

There are a number of exon and intron sequences that are very small in size (see, for example, introns 25507-25384 (intron 5), 25287-21169 (intron 6) and exons 2 (36384-36310) and 29565-29615 (exon 4)). It is Applicant's assertion that one of ordinary skill in the art would not have a reasonable expectation of success of actually identifying these particular sequences, particularly, what constitutes intron and exon sequences.

Applicant also notes that there has been a great deal of interest in the scientific community in MDM2 given its potential use as a diagnostic and therapeutic agent. This interest is summarized in the cited patent, Vogelstein et al. However, there was absolutely no disclosure or suggestion of the genomic organization of MDM2 genomic DNA until the instant application was filed. An independent disclosure of the genomic organization of the MDM2 gene was not available until July 21, 2004, more than one year after the filing date of the instant application (Liang et al., 2004, Gene 338:217-223). The Court of Customs and Patent Appeals (CCPA) and its present successor, the Court of Appeals for the Federal Circuit (CAFC), have held the following considerations to be objective evidence of nonobviousness; long felt need, commercial success, failure of others, copying and unexpected results. *In re Sernaker*, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983); *In re Imperato,* 179 U.S.P.Q. 710 (CCPA 1973).

It is asserted that the state of the art provides various techniques for obtaining genomic DNA using cDNA probes that are usually labeled and that the comparison of genomic and cDNA would result in the identification of non-coding regions. However, there is nothing stated in the Office Action as to how the state of the art teaches how given the teaching of a large genomic clone and the cDNA sequence of a particular gene, one of ordinary skill in the art could with particularity identify specific exon and intron sequences of a particular gene and assemble it in its entirety. There is no prior art that defines the complete genomic structure of a particular gene. This is necessary in order to accurately identify the claimed noncoding sequences in the instant invention.

At best, it would be an obvious to try situation. An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d

1741 (Fed. Cir. 1990). "Obvious to try" has long been held not to constitute obviousness. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed.Cir.1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel* 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). Here, only a general incentive at best was provided.

In view of the above arguments, it is asserted that claims 7, 10, and 15-20 are not obvious over the cited references. In addition, new claims 23-31 are not obvious over the cited references. Therefore, Applicants respectfully request that the rejections be withdrawn.

7. Response to the Examiner's Interview Summary

Applicant would like to thank Examiner Slobodyansky for her time and useful suggestions made during her interview with Applicant's Representative, Cheryl H. Agris on February 22, 2005. The pending claims and current Office Action were discussed. The Interview Summary dated February 24, 2005 states:

> It appears that the amendment of Claim 7 is not relevant to the outstanding rejection because it is related to non-elected 5' and 3' regions. Therefore, the 112, 1st paragraph rejections and 103 rejection would remain. It was explained why limiting the claims to the fragments of non-coding region (e.g., exon-intron sequence) as opposed to the sequences that hybridize thereto will NOT overcome the 103(a) rejection.

In response, the amendment of claim 7 is relevant to the outstanding rejection since it does contain recitation of the elected species, encompassed by the recitation of "contiguous exon-intron sequence" and "contiguous intron-exon sequence". Applicant does note for Examiner's reference that claim 24, directed to an isolated nucleic acid molecule consisting of at least 20 nucleotides unique to a reverse or forward strand of a contiguous exon-intron region or a contiguous intron-exon region.

Applicant agrees that the 35 U.S.C. 103(a) rejections were discussed. However, as stated during the interview and as further argued above, it is Applicant's belief that the claimed nucleic acid molecule is not obvious over the cited references. Applicant respectfully requests that the Examiner reconsider the rejection in view of the arguments set forth above.

8. Conclusion

In view of the foregoing, Applicants assert that the claims are now in condition for allowance. Early action to that end is respectfully requested. The Examiner is invited to contact the undersigned at (914) 712-0093 if she has any questions.

Respectfully submitted,

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